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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/071,962
Filing Date: February 08, 2002
Appellant(s): NI ET AL.

Cheryl A. Liljestrand
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/10/2006 appealing from the Office action mailed 1/9/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: Claims 31-33, 36-38, 40, 45 and 48-50 are rejected under 35 U.S.C. §**102(b)** as being anticipated by Cunningham et al., US Patent No. 5,506,107, not under 35 U.S.C. §103(a) as (mis)stated by appellants.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix filed 1/22/2007 to the brief filed 10/10/2006 is correct.

(8) Evidence Relied Upon

5,506,107	Cunningham et al.	4/9/1996
6,342,220	Adams et al.	1/29/2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31-33, 36-38, 40, 45 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al., US Patent No. 5,506,107.

Cunningham et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. At columns 23-24, Cunningham et al. discuss agonist antibodies to the growth hormone receptor, and state that such antibodies may be raised by immunizing animals against growth hormone (and presumably screening the resultant antibodies for agonist properties). Also at columns 23-24, Cunningham et al. disclose such antibodies to be monoclonal, chimeric, or CDR grafted, and compositions comprising such antibodies. The person of ordinary skill in the art would immediately grasp CDR grafted antibodies as disclosed by Cunningham et al. as meaning humanized, as in claim 50. The screening methods for identification of agonist antibodies are disclosed at columns 36-39. At column 23, Cunningham clearly states:

We have determined that certain antibodies are capable of stimulating the hGH receptor, i.e., they are capable of crosslinking the receptors in a fashion that mimics the ability of hGH to form a ternary complex and activate the receptor. Examples of such agonist antibodies were already known at the time of this invention, but their ability to act as agonists of hGH was unappreciated. Suitable antibodies are MAb 263 (Barnard, et al., Endocrinology, 115:1805-1813 [1984] or Barnard, et al., Biochem. J., 231:459-468 [1985]). Others are MAbs 13E1 and 3D9, produced by methods described below.

Further, Cunningham confirmed the agonist antibody activity *in vivo*, see column 36.

Thus, Cunningham clearly not only discloses **having** such antibodies, but that they were already available in the prior art. The Examiner notes that determination of a property of a compound that was already known does not make the compound newly patentable, as a compound and its properties are inseparable.

Thus, Cunningham discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims, and that such methods were successful in obtaining said antibodies. Accordingly, Cunningham et al. is clearly anticipatory, and fairly placed the claimed invention in the hands of the public.

Claims 31-33, 36-38, 40, 45 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al., US Patent No. 6,342,220.

Adams et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. Fragment and single chain antibodies are discussed at column 18. Methods of making the antibodies are disclosed at column 25. Thus, Adams discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Adams et al. fairly place the claimed invention in the hands of the public.

(10) Response to Argument

With respect to the rejection of Claims 31-33, 36-38, 40, 45 and 48-50 under 35 U.S.C. 102(b) as being anticipated by Cunningham et al., US Patent No. 5,506,107:

At page 6 of the appeal brief, appellants argue that Cunningham is not an enabling reference because it did not disclose any anti-GCSF (sic) agonist antibodies, and cite an office action written by this Examiner in the parent case, 09/303155 as an admission by the Examiner of such "fact". This argument has been fully considered but is not deemed persuasive because the action in the parent case was clearly in error. An error six years ago by the Examiner does not negate the fact that Cunningham *clearly teaches having made antibodies within the scope of the present claims;* see quotation from the Cunningham patent, above.

Also at page 6, appellants argue that it is difficult to obtain agonist antibodies, and that the Cunningham reference is therefore not enabling. This argument has been fully considered but is not deemed persuasive because :

a) The Cunningham reference actually obtained the claimed antibodies, and is an anticipatory reference. Accordingly, arguments as to how hard it *might* be to obtain the antibodies and the unpredictability of doing so are not pertinent.

b) The Schneider paper I) is not the closest prior art, as it is not related to G-CSF itself, but to EPO, the receptors for which are quite distinct, II) Schneider et al. actually obtained an agonist antibody, out of 48 screened (according to appellant's characterization of the paper), clearly demonstrating that it did not require undue experimentation to find such antibodies.

c) Appellants then go on to discuss a declaration by Baufo Ni, submitted 12/17/2001 in parent application 09/303155, which declaration has *not* been made of record in this case. However, for the convenience of the Board, the Examiner provides the response to that declaration as found in the advisory action dated 1/4/2002 in Application Serial Number 09/3031545 as an appendix to this Examiner's Answer. Note also that the rejection in the parent case was under 35 U.S.C. §103 on the basis of obviousness, and not under 35 U.S.C. §102 on the basis of anticipation, as is the case here. It is well established that "unexpected" results are ineffective in overcoming a finding of anticipation.

Thus, it remains that Cunninham is enabling and anticipatory of the rejected claims.

At page 8 of the brief, appellants argue that Cunningham does not anticipate claim 49, as Cunningham discloses no sequences, and as Cunningham does not disclose the specific antibodies mAB166-93 or mAb174-24-11. This argument has been fully considered but is not deemed persuasive. See the Office Action mailed 1/09/2006, page 2, in the section labeled "claim interpretation", which states:

> The language of claim 49 states in part "The agonist antibody of claim 31 wherein the antibody comprises…" "a functional variant of any one of SEQ ID NOs 15 to 20. This allows variation in all six CDRs, and thus reads on any agonist antibody that binds human G-CSF. [1]

Thus, the Examiner clearly made of record that the claim is interpretated as reading on any functionally equivalent antibody. As the sole relevant disclosed properties of antibodies mAB166-93 or mAb174-24-11 are that they are agonist antibodies, the agonist antibodies of Cunningham et al. fairly anticipate the claim.

With respect to the rejection of Claims 31-33, 36-38, 40, 45 and 48-50 under 35 U.S.C. 102(b) as being anticipated by Adams et al.:

At page 8 of the Appeal Brief, Appellant argues that there is no disclosure in the Adams reference of making G-CSF agonist antibodies. This argument has been fully considered but is not deemed persuasive. As stated in the rejection above, Adams et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56.

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[1] The Examiner has reproduced only the relevant portion of the claim interpretation section. The other text is: "Newly submitted claim 48 contains a product-by-process limitation regarding how the antibody was made. While not *per se* indefinite, it is noted that product-by-process limitations are given weight only to the extent that the affect the product being claimed. Antibodies are generally considered to be fully defined by their binding properties, in this case to "specifically bind(s) or interact with human G-CSF receptor" (although the latter limitation is itself indefinite, see below), thus making the product-by-process limitation irrelevant."…"With regard to claim 50, "framework" is an inherent [1]part of the structure of an antibody, and accordingly requires no antecedent basis in the independent claim."

Specifically, there are two paragraphs of Adams et al. that lead directly to the claimed invention; the first is found at column 11, line 51 and states:

"Agonist antibodies" (aAb) are antibodies or fragments thereof that possess the property of binding to a cytokine superfamily receptor and causing the receptor to transduce a survival, proliferation, maturation and/or differentiation signal. Included within the definition of transducing a survival signal is a signal which modulates cell survival or death by apoptosis. To be therapeutically useful the agonist antibodies of this invention will be capable of inducing or causing survival, proliferation, maturation or differentiation at a concentration equal to or not less than 2 orders of magnitude (100-fold) below that of the natural in vivo ligand on a weight basis.

The second is found at column 12 line 54 and states:

"Cytokine superfamily receptors" and "hematopoietic growth factor superfamily receptors" are used interchangeably herein and are a group of closely related glycoprotein cell surface receptors that share considerable homology including frequently a WSXWS domain and are generally classified as members of the cytokine receptor superfamily (see e.g. Nicola et al., Cell, 67:1-4 (1991) and Škoda, R. C. et al. EMBO J. 12:2645-2653 (1993)) Generally, these receptors are interleukins (IL) or colony-stimulating factors (CSF). Members of the superfamily include, but are not limited to, receptors for: IL-2 (b and g chains) (Hatakeyama et al., Science, 244:551-556 (1989); Takeshita et al., Science, 257:379-382 (1991)), IL-3 (Itoh et al., Science, 247:324-328 (1990); Gorman et al., Proc. Natl. Acad. Sci. USA, 87:5459-5463 (1990); Kitamura et al., Cell, 66:1165-1174 (1991a); Kitamura et al., Proc. Natl. Acad. Sci. USA, 88:5082-5086 (1991b)), IL-4 (Mosley et al., Cell, 59:335-348 (1989), IL-5 (Takaki et al., EMBO J., 9:4367-4374 (1990); Tavernier et al., Cell, 66:1175-1184 (1991)), IL-6 (Yamasaki et al., Science, 241:825-828 (1988); Hibi et al., Cell, 63:1149-1157 (1990)), IL-7 (Goodwin et al., Cell, 60:941-951 (1990)), IL-9 (Renault et al, Proc. Natl. Acad. Sci. USA, 89:5690-5694 (1992)), granulocyte-macrophage colony-stimulating factor (GM-CSF) (Gearing et al., EMBO J., 8:3667-3676 (1991); Hayashida et al., Proc. Natl. Acad. Sci. USA, 244:9655-9659 (1990)), **granulocyte colony-stimulating factor (G-CSF)** (Fukunaga et al., Cell, 61:341-350 (1990a); Fukunaga et al., Proc. Natl. Acad. Sci. USA, 87:8702-8706 (1990b); Larsen et al., J. Exp. Med.,

172:1559-1570 (1990)), EPO (D'Andrea et al., Cell, 57:277-285 (1989); Jones et al., Blood, 76:31-35 (1990)), Leukemia inhibitory factor (LIF) (Gearing et al., EMBO J., 10:2839-2848 (1991)), oncostatin M (OSM) (Rose et al., Proc. Natl. Acad. Sci. USA, 88:8641-8645 (1991)) and also receptors for prolactin (Boutin et al., Proc. Natl. Acad. Sci. USA, 88:7744-7748 (1988); Edery et al., Proc. Natl. Acad. Sci. USA, 86:2112-2116 (1989)), growth hormone (GH) (Leung et al., Nature, 30:537-543 (1987)), ciliary neurotrophic factor (CNTF) (Davis et al., Science, 253:59-63 (1991) and c-Mpl (M. Souyri et al., Cell 63:1137 (1990); I. Vigon et al., Proc. Natl. Acad. Sci. 89:5640 (1992)).

Since Adams et al. disclose making agonist antibodies to cytokine superfamily receptors, and specifically list the G-CSF receptor as being one of those receptor, appellant's argument is not factually correct.

Bridging pages 9-10, appellants argue that Adams is non-enabling prior art. This argument has been fully considered but is not deemed persuasive because appellants have provided no fact or evidence to establish that Adams is non-enabling. To the contrary, the evidence of record, in the form of Cunningham et al., clearly demonstrates that no more than routine experimentation is required to obtain antibodies as disclosed by Adams. The Examiner notes the decision *In re Graves*, 36 USPQ 2d1697 at 1701 which held that a reference. anticipates a claim if it discloses the claimed invention "such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." Clearly this is the case with the Adams reference.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Argument

Should appellants request an oral hearing, the Examiner respectfully requests to attend to present arguments.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Lorraine M. Spector, Ph.D.
Primary Examiner

Conferees:

Brenda Brumback
Quality Assurance Specialist

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Quality Assurance Specialist

APPENDIX

RESPONSE TO NI DECLARATION FROM PARENT APPLICATION 09/303155, (PAPER NUMBER 19) MAILED 1/04/2002

Serial Number 09/303155
Attachment to Advisory Action, paper number 19:

The declaration under 37 37 C.F.R. § 1.132 by Dr. Ni filed 12/10/01 is insufficient to overcome the rejection of claims 31-36, 39 and 42 under 35 U.S.C. §103(a) based upon Cunningham as set forth in the last Office action because:

The statement at paragraph 5 that the Cunningham disclosure at column 12, line 56 is not relevant to the claimed invention is a legal conclusion, and is not persuasive. More to the point, that portion of the Cunningham patent was cited as evidence that Cunningham disclosed the desirability of making agonists which stimulate the G-CSF receptor. The fact that such was in the context of a discussion of making peptide agonists and not antibody agonists does not detract from that teaching.

At paragraph 7, declarant states that there are several reasons why Cunningham's hybrid receptor method would not have been successful for isolation of a G-CSF receptor agonist: This conclusory statement is on the basis that at the rate at which applicants obtained potential agonist antibodies, 10 from 500,000 potential candidates, measuring ^{3}H-thymidine incorporation would not have been practical, on the basis of cost and "risk of radioactive contamination". This argument has been fully considered but is not deemed persuasive because the standard applied under 35 U.S.C. §103(a) is not cost or risk of contamination, but whether the claimed invention would have been obvious over the cited prior art, and whether the guidance in the cited prior art, taken in view of the art as a whole at the time the invention was made, would enable one of ordinary skill in the art to make the claimed invention with a reasonable expectation of success. Cunningham et al. claim a screening method to determine whether a candidate compound is a potential agonist (see claim 8, for example), and clearly state at column 36 that "The assay of the present invention may be used to screen monoclonal antibodies that are directed against growth hormone receptors. The resulting monoclonal antibodies can then be evaluated in vivo for relative ability to promote growth." This, taken with the teaching at column 12 that agonists of G-CSF are also envisioned, as further evidenced by the claims themselves that screening for G-CSF agonists is part of the invention (claim 11) would lead to an expectation of success. Claim 8 of Cunningham et al. does not rely on ^{3}H-thymidine as a detection method, nor are cost or risk of contamination valid arguments against a reasonable

expectation of success. Further at paragraph 7, declarant argues that use of a hybrid receptor detection system is "not sufficiently predictive of a true agonist". This argument has been fully considered but is not deemed persuasive because Cunningham et al. clearly indicate at column 36 that their claimed assay is for preliminary identification of agonists, and that "(T)he resulting monoclonal antibodies can then be evaluated in vivo for relative ability to promote growth." Thus, one of ordinary skill in the art reading Cunningham's disclosure would have known that an *in vivo* confirmation of agonist activity would have been necessary.

At paragraphs 8-9 declarant argues that the rarity of actual agonist antibodies overcomes the conclusion of obviousness based upon Cunningham et al. This argument has been fully considered but is not deemed persuasive because with respect to the search for EPO agonists by Schneider et al. as cited by declarant, although 47 of the 48 putative agonist antibodies may not have been confirmed by the in vivo assay, one of the 48 (by subtraction) was confirmed as such. Accordingly, it would appear that Schneider et al. support the finding of obviousness, in that no undue experimentation was required to obtain an EPO-agonist antibody. The Examiner's position is supported by the case law. The decision in *In re O'Farrell*, 7 USPQ2d 1673 at 1681 summarized the issue succinctly. The paragraphs from the *O'Farrell* decision read, in their entirety, as follows:

> [3] The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industry A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). Neither of these situations applies here.

> [4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. In re Merck & Co ., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co ., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch , 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. In re Longi , 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); In re Clinton , 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success.

Following the logic therein, as the prior art, Cunningham et al., teach the desirability of G-CSF agonists, teach that antibody agonists are desirable, and teach methods of screening for such agonists, along with an expectation of success at doing so, and as the prior art cited by declarant appears to support the predictability of finding such agonists without undue experimentation, the Examiner maintains the finding of obviousness. The Examiner further finds the instant situation to be analogous to that in *In re Wands* (CAFC) 8 USPQ2d 1400 , 1988, which was drawn to screening of hybridoma cells for those producing desired antibodies. In *Wands*, there were adequate teachings of how to obtain such hybridoma cells and a reasonable expectation of success at obtaining ones expressing the desired antibodies, the specification having shown nine of 143 such isolates to meet the limitations of the claims. Applicants have presented no facts or evidence that undue experimentation would be required to obtain G-CSF agonist antibodies following the teachings of Cunningham et al., that is, undue as compared to the 'odds' in the *Wands* case, Thus, this remains an instance of merely routine screening, and the declaration fails to overcome the *prima facie* finding of obviousness over Cunningham et al.

LORRAINE SPECTOR
PRIMARY EXAMINER